



# THE MITOCHONDRIAL SUGAR DISEASE AND MOLECULAR MECHANISM

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## ABSTRACT

Mitochondria are the power factories of the cells and produce ATP by oxidizing reducing equivalents via the respiratory chain.

These reducing equivalents originate mainly from the citric acid cycle that also occurs within the mitochondria. Human mitochondria contain their own genetic material in the form of circular DNA that encodes for only a fraction of the mitochondrial components. The other mitochondrial components are nuclear encoded.

Furthermore, the respiratory chain and mitochondrion associated monoamine oxidase are major producers of reactive oxygen radicals. As a result, mutations in mtDNA can deregulate multiple processes within cells and the balance of this deregulation may contribute to the clinical phenotype Mitochondrial diabetes affects up to 1% of patients with diabetes and is often unrecognized by the physicians.

Diabetes and deafness (DAD) or maternally inherited diabetes and deafness (MIDD) or mitochondrial diabetes is a subtype of diabetes which is caused from a point mutation at position 3243 in human mitochondrial DNA, which consists of a circular genome. This affects the gene encoding tRNA<sup>Leu</sup>. Diabetes mellitus is a common feature of mitochondrial disease, but rarely occurs in isolation; other clinical features depend largely on the underlying mtDNA or nuclear DNA mutation.

Because mitochondrial DNA is contributed to the embryo by the oocyte and not by spermatozoa, this disease is inherited from maternal family members only. As indicated by the name, MIDD is characterized by diabetes and sensorineural hearing loss. As suggested by the name, patients with MIDD are subject to sensorineural hearing loss. MIDD has also been associated with a number of other issues including kidney dysfunction, gastrointestinal problems, and cardiomyopathy.

**KEYWORDS:** Diabetes and deafness (DAD), Sensorineural hearing loss. Cardiomyopathy, Adenosine deaminase, Glucokinase gene in type 2 diabetes mellitus, Maternally inherited diabetes and deafness (MIDD), Retinal vascular disease, Gluconeogenesis Introduction MtDNA disorders were originally thought to be rare causes of neurological disease.

It is difficult to estimate the true prevalence of mtDNA disease because of the clinical and genetic heterogeneity, as well as the likely under diagnosis in clinical practice. Current prevalence figures for the northeast of England are a minimum of 9.2 per 100,000 of the population (1)

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia resulting from autoimmune destruction of  $\beta$  cells (beta cells) of pancreas and genomic deoxyribonucleic acid (DNA) mutations in the gene linked to insulin, insulin receptor, enzyme adenosine deaminase, and glucokinase gene in type 2 diabetes mellitus (2)

Genetic defects seem to be involved both in glucose induced insulin secretion and peripheral insulin sensitivity. Patients who would develop T2DM at later stages of their life, due to some genetic cause, have a decreased insulin response and impaired glucose tolerance even in preclinical period (3)

Changes in the intracellular ATP/ADP ratio, due to oxidative phosphorylation in the mitochondria, trigger the exocytosis of insulin containing secretory granules (4)

Diabetes mellitus manifests as several clinical entities characterized by chronic hyperglycaemia. Glucose homeostasis is maintained via a glucose sensor in the

pancreatic  $\beta$ -cell that detects blood glucose elevation, prompting insulin secretion by the  $\beta$ -cell. Increased circulating insulin concentrations suppress the hepatic glucose output and stimulate glucose uptake by skeletal muscle and adipose tissue (5)

The pathophysiological mechanisms leading to diabetes include inappropriate insulin secretion; insulin resistance of the liver, skeletal muscle, and fat; or combined defects.

Autoimmune type 1 diabetes and common type 2 diabetes (T2D) are polygenic syndromes (6)

Diabetes is a serious, long-term condition with a major impact on the lives and well-being of individuals, families, and societies worldwide. It is among the top 10 causes of death in adults, and was estimated to have caused four million deaths globally in 2017 (7)

Maternally inherited diabetes and deafness (MIDD) (OMIM # 520000) is a rare form of diabetes that results, in most cases, from an A-to-G transition at position 3243 of mitochondrial DNA (m.3243A>G) in the mitochondrial-encoded tRNA leucine (UUA/G) gene. Besides this point mutation, there are other less frequent variants also associated with MIDD (8)

Impairment of insulin secretory capacity was demonstrated in individuals carrying the m.3243A>G mutation, possibly the primary defect contributing to the development of diabetes mellitus (9)

The molecular mechanisms responsible for the development of this insulin-requiring diabetes are complex and seem to be related to beta-cells dysfunction, loss of beta-cells mass and insulin deficiency (10)

India is home to over 74 million diabetics, and the number is estimated to exceed 123 million, by 2040 (11)

Increasing longevity, changing lifestyle and dietary habits contribute to increasing prevalence of diabetes mellitus (DM) in India and all over the world (12)

Increase in the disease burden (among all non-communicable diseases) between the year 1996 and 2016 was noted for DM at 80% (13)

Diabetes and its complications are now an area of focus for prevention of mortality and morbidity. Absence of acute symptoms and lack of awareness are the main barriers for detection of DM and its complications (14)

Much like finding a needle in a haystack, the identification of patients with monogenic forms of diabetes mellitus (DM) is challenging and potentially costly. Nonetheless, the importance of identifying such individuals with monogenic forms of diabetes has been underscored by the recognition that response to therapy is different from individuals with type 1 and type 2 DM (15).

Metformin, the most commonly used first-line medication for type 2 DM, may cause lactic acidosis in individuals with pathogenic mitochondrial DNA mutations (16).

Mutations in mitochondrial DNA cause a number of neurological diseases with defined neuropathology; however, mutations in this genome have also been found to be important in a number of more common neurodegenerative diseases. (17)

Maternally inherited diabetes and deafness (MIDD) and Ballinger-Wallace syndrome is due to mitochondrial mutations and also has a dominant inheritance pattern. It is a sub type of diabetes characterized by maternal inheritance of diabetes and neurosensory deafness caused by variation in the mitochondrial tRNA gene at position 3243 (18)

Investigation of mitochondrial disorders requires an integrated approach, such as clinical, biochemical, histological and genetic for unambiguous diagnosis. Simple biochemical examinations of blood would provide very efficient and supporting evidence for clinical investigation (19)

It was originally considered that the main defect leading to diabetes is an altered glucose metabolism of muscle. (20)

#### HISTORY:

Diabetes was one of the first diseases described, with an Egyptian manuscript from c. 1500 BCE mentioning "too great emptying of the urine." (21)

The Ebers papyrus includes a recommendation for a drink to take in such cases. The first described cases are believed to have been type 1 diabetes (22)

Indian physicians around the same time identified the disease and classified it as madhumeha or "honey urine", noting the urine would attract ants (23)

The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Apollonius of Memphis. The disease was considered rare during the time of the Roman empire, with Galen commenting he had only seen two cases during his career (24)

Major Discoveries in Mitochondrial Diabetes With explosive increase in its prevalence, diabetes mellitus, as a clinical medical disorder, is to be reckoned on par with hypertension and atherosclerosis. A versatile disease diabetes, in view of its frequent clinical and epidemiological link, with other two constituents a health problem of paramount concern for a very large proportion of world population.

Patients with variable degree of hyperglycaemia and sensory hearing impairment. There is a maternal inheritance of diabetes ie diabetes will only be transmitted by females. In presence of such history, the diagnosis should be entertained and it can be confirmed in most cases by a molecular genetic analysis Mitochondrial disorders. Mitochondria are present in all tissues and dysfunction causes wide spread effects on vision (optic atrophy, retinitis pigmentosa, cataracts), hearing loss (sensory neural deafness) and the endocrine, cardiovascular, gastrointestinal and renal systems. Any combination of these should raise the suspicion of a mitochondrial disorder, especially if there is evidence of maternal transmission. Mitochondrial dysfunction can be caused by alterations in either mitochondrial DNA or genes encoding for oxidative processes, genetic abnormalities or mutations in mitochondrial DNA may affect single individuals and single tissues (Most commonly muscle) Thus patients with exercise intolerance

and myalgia and sometimes recurrent myoglobinuria may have isolated pathogenic mutations in genes encoding for oxidation pathways. Inherited disorders of oxidative pathways of the respiratory chain in mitochondria cause a group of disorders, either restricted to the muscle or associated with non-myopathic features. Many of these mitochondrial disorders are inherited via mitochondrial genome down the maternal line. Mutations may be due to either to point mutations or deletions of mitochondrial DNA (25)

Hearing loss, as caused by the 3243 mitochondrial DNA mutation, is seen in the form of progressive cochlear dysfunction.

As the mutation in the tRNA<sup>Leu</sup> (UUR) leads to unbalanced amounts or unstable respiratory chain enzymes, respiration and oxidative phosphorylation are reduced, leading to lower levels of ATP (26)

Naturally, the most metabolically active organs in a person will be affected by this ATP deficiency. The hair cells, both essential to sound transduction, make use of ion pumps to regulate the concentration of ions including K<sup>+</sup>, Na<sup>+</sup>, and Ca<sup>2+</sup> using ATP (27)

Neurodegeneration Caused by Primary Mitochondrial DNA Abnormalities MtDNA defects take the form of large-scale rearrangements (usually deletions) or point mutations.

Reduced action of insulin on cardiac cells diminishes the uptake efficiency of glucose, which reduces the glucose utilization and limits the oxygen consumption for ATP synthesis and finally develops the state of cardiomyopathy. There are two mechanisms that govern the cardiovascular dysfunctioning and development of cardiovascular disorders during mitochondrial diabetes.

#### DIFFERENTIAL CLINICAL CHARACTERIZATION OF mtDB FROM OTHER FORMS OF DIABETES:

mtDB has maternal transmission of disorder & surely gets transmitted to zygote where mother is a mt-diabetic patient while this is not a case with T1D, T2D or MODY form of diabetes.

A3243G mutation results in phenotype similar to T1D and includes impaired insulin secretion, altered glucose metabolism in skeletal muscle and increased gluconeogenesis due to overproduction of lactate; however it can be differentiated based on inheritance pattern, genetic screening and age of onset. In some patients if the age of onset is similar to T1D, then it can be misdiagnosed but the person will not show the characteristic antibodies associated with autoimmune T1D. Development of clinical disorders like cardiac dysfunctioning, MELAS syndrome, deafness etc.

mtDB is different from MODY because of maternal inheritance and co morbidities like cardiomyopathy, renal failure, deafness and MELAS. (28)

Gene variants that have been identified to contribute to the major forms of diabetes, such as autoimmune type 1 diabetes and metabolic syndrome-associated type 2 diabetes, are "low penetrance" variants that modulate the susceptibility of an individual to develop diabetes or that protect against the disease (29)

These so-called monogenetic forms of diabetes comprise the various forms of maturity-onset diabetes of the young (MODY) and mitochondrial diabetes, also called "maternally inherited diabetes and deafness (30)"

#### Symptoms of mitochondrial diabetes:

Poor growth, loss of muscle coordination, muscle weakness, hearing problems, learning disabilities, heart disease, liver disease, kidney disease, gastro intestinal disorders, respiratory disorders and retinopathy. Retinopathy is any damage to the retina of the eyes, which may cause vision impairment. Retinopathy often refers to retinal vascular disease, or damage to the retina caused by abnormal blood flow. Age-related macular degeneration is technically included under the umbrella term retinopathy but is often discussed as a separate entity.

Retinopathy, or retinal vascular disease, can be broadly categorized into proliferative and non-proliferate types. Frequently, retinopathy is an ocular manifestation of systemic disease as seen in diabetes or hypertension. Acquired conditions in which mitochondrial dysfunction has been involved are Huntington's disease, cancer, Alzheimer's disease, Parkinson's disease, bipolar disorder, [schizophrenia, aging and senescence, anxiety disorders.

Although the prevalence of these varieties of diabetes would vary in various ethnic groups, it is estimated that they do not make more than about 5% to 10% of young age diabetes. Some rare genetic abnormalities described are insulin gene abnormality which produces an abnormal insulin or a convertage deficiency which impairs the conversion of pro insulin to insulin.

#### Pathophysiological mechanisms leading to diabetes:

Additional studies did not identify insulin resistance as a common factor in most carriers of the A3243G mutation, although insulin resistance has been reported in some carriers. Furthermore, energy metabolism in muscle, as reflected by ATP/ADP and phosphocreatine levels under conditions of rest

and exercise, is not strongly deregulated Hepatic glucose production may be another factor that becomes deregulated by the A3243G mutation.

A mitochondrial dysfunction in muscle is expected to lead to a higher lactate flux to the liver, fueling gluconeogenesis. At this time, no data are available on hepatic glucose production and its suppression by insulin in carriers of the A3243G mutation. Mutations in mitochondrial DNA (mtDNA) associate with various disease states.

A few mtDNA mutations strongly associate with diabetes, with the most common mutation being the A3243G mutation in the mitochondrial DNA-encoded tRNA(Leu,UUR) gene. This article describes clinical characteristics of mitochondrial diabetes and its molecular diagnosis. Furthermore, it outlines recent developments in the molecular mechanisms leading to a diabetic state.

A gradual development of pancreatic  $\beta$ -cell dysfunction upon aging, rather than insulin resistance, is the main mechanism in developing glucose intolerance. Carriers of the A3243G mutation show during a hyperglycemic clamp at 10 mmol/l glucose a marked reduction in first- and second-phase insulin secretion compared with non-carriers.

Other rarer forms of monogenic diabetes Wolfram syndrome is rare recessive disorder caused due to mutations in WFS1 gene, characterized by combination of familial juvenile onset diabetes mellitus, optic atrophy, diabetes insipidus and deafness. Friedrich's ataxia is an autosomal recessive condition due to mitochondrial dysfunction caused by deficiency of FRDA gene encoding frataxin which leads to ataxia. It is associated with hypertrophic cardiomyopathy, blindness, deafness and diabetes mellitus. Pearson marrow pancreas syndrome is due to the large portion of mitochondrial DNA and characterized by type-1 diabetes mellitus, anemia, exocrine pancreatic dysfunction and failure to thrive. Kearns-Sayre syndrome is also due to deletion of portion of mitochondrial DNA manifesting with diabetes mellitus, cardiomyopathy and retinal degeneration Diagnosis of Mitochondrial diabetes. CK may show increased level in many cases, but is often found in normal range.

However, presence of elevated CSF lactate together with seizures and stroke like episodes are highly suggestive of mitochondrial disorder and such results should be interpreted with caution (31)

Although high levels of mutations can be detected in blood, it is always advisable to use skeletal muscle for detecting mtDNA mutations, especially for deletions or mtDNA rearrangements.(32)

Depletion of mtDNA can be detected by real-time PCR, which is also indicative of nuclear gene mutations, predominantly present in infants with myopathy or hepatocerebral phenotype (33)

However, due to highly polymorphic nature of the mitochondrial genome, care must be taken before assigning pathogenicity to a novel mtDNA variant

#### Life style modifications in management of diabetes:

Our ancient ayurvedic physicians Susruta and Charaka stressed on the role of exercise in the treatment of diabetes. even after the advent of insulin, Joslin emphasized the importance of exercise as one of the basic principles of management of diabetic patients. The goal of dietary therapy is to provide a nutritionally balanced diet to maintain the ideal body weight (IBW) of patient to achieve good glycaemic control along with correction of the dyslipidemia.

The dietary planning is based on the type of diabetes, weight of the patient, activity, profile and presence of co-morbid conditions. Indian diets traditionally are high carbohydrate content. There have been concerns expressed regarding difficulty in achieving glycaemic control and an increase in the development of complications with such diets. However studies from India, Japan have shown that even with diet high in carbohydrate content, good glycaemic control can be achieved without increasing the risk of complications.

Adequate physical activity helps in correcting obesity which is a major modifiable risk factor. In addition, physical activity may independently enhance insulin sensitivity and glucose tolerance. Exercise increases the skeletal glucose transporter protein GLUT4 which is responsible for insulin independent glucose transport into skeletal muscle.

Several recent studies have documented the beneficial effect of yogic practices improve glycaemic control, reduce BP, correct dyslipidaemia reduce insulin resistance and eliminate stress leading to effective control of diabetes and prevention of its long term complications (34)

#### TREATMENT:

Exercise training's mostly aim to improve the physical capacity and quality of life in patients by enhancing the mitochondrial function, and decreasing the burden of unhealthy mitochondria.

Several studies have shown that the reversal of a sedentary lifestyle in mitochondrial disease with exercise therapy confers benefits to mitochondrial function by

improved OXPHOS activity. Also, the benefit of endurance exercises on COX10 knockout mice showed delay in the disease onset, increased ATP levels, OXPHOS activity, and life expectancy. (35)

Caloric needs for the patients with mitochondrial disease are mostly altered compared to normal individuals.

Optimizing the quantity and quality of calories has been shown to improve the mitochondrial health in patients (36)

The ketogenic diet (KD) is a high fat and low glucose diet, which stimulates lipid utilization by mitochondrial beta oxidation and ketone body production in the liver. KD has been used for many years in children suffering from seizures, who are mostly resistant to conventional antiepileptic drugs (AEDs) (37).

The use of KD has been shown to improve the brain energy metabolism by upregulating mitochondrial biogenesis, inhibiting ROS production, increasing neuron glia interaction and ATP concentration (38)

The use of KD has been shown to shift the level of heteroplasmy in cells harbouring mtDNA deletion.

These studies suggest the potential usefulness of KD in treatment of mitochondrial diseases. However, more controlled trials on patients and better elucidation of its mechanism are still warranted (39)

The rationale for using cocktails of vitamins and co-factors is more compelling, when factors in question are decreased either due to deficiency or defect in their transport; for example, diseases due to carnitine or CoQ10 deficiency (40)

Coenzyme Q10 (CoQ10) also known as ubiquinone, has been widely used for the treatment due to its well documented safety and lack of negative side effects even at higher concentrations. The most favourable property of CoQ10 is its dual role as a component of the respiratory chain and one of the most potent ROS scavengers. Despite the beneficial effects and widespread use of CoQ10 in mitochondrial diseases, controlled trials of this drug on large cohorts of patients are still missing.

The supplementation of CoQ10 showed positive results in patients with primary or secondary CoQ10 deficiency and is advisable to be tried in all patients with decreased CoQ10 concentration (41)

Creatine is used extensively as an energy boosting compound for the treatment of mitochondrial disorders. A randomized, controlled trial in adult patients with mitochondrial cytopathies showed benefit from creatine intake at an initial dose of 5 g twice a day for two weeks followed by 2 g twice a day for one week. A study exploring the effect of the three compounds showed a different mechanism of action, i.e. (CoQ10 and creatine) increased ATP production, (CoQ10 and lipoic acid) scavenging ROS, while only creatine provided an alternative energy source. Given the conflicting results on the use of creatine alone, it is always advisable to give creatine in combination with CoQ10 in patients showing positive response with these supplements (42)

L-Arginine is a semi-essential amino acid, involved in growth, urea detoxification, and creatine synthesis.

An initial small study demonstrated that intravenous administration of L-arginine (500 mg/kg/dose) decreased the severity of stroke like symptoms, enhanced the dynamics of microcirculation, and reduced tissue injury from ischaemia in patients with MELAS. In a large study, a decrease in clinical severity and frequency of stroke like events was demonstrated in MELAS patients, who were treated prophylactically with oral L-arginine (150-300 mg/kg/d)

However, randomized controlled trials are required to study the effects of L-arginine in treatment of mitochondrial strokes (43)

Carnitine is a cellular compound that plays a critical role in the process of fatty acid oxidation and esterification of fatty acids by transferring long-chain fatty acids across the mitochondrial inner membrane as acyl carnitine esters.

While L-carnitine supplementation is mostly used in patients with mitochondrial disorders to restore free carnitine levels but is rarely used alone. Mostly L-carnitine is used either with valproic acid as it inhibits the carnitine uptake when used alone, or is used together with CoQ10 (44)

Dichloroacetate (DCA) is more specifically used as a lactic acid lowering agent.

It activates the pyruvate dehydrogenase complex by inhibiting the activity of the pyruvate dehydrogenase kinase, which normally phosphorylates and inhibits the enzyme DCA has the ability to keep the pyruvate dehydrogenase complex in an active state, which reduces the accumulation of lactate in body tissues. There have been multiple reports about the use of DCA with various degrees of success in lowering the lactic acid level.

In a controlled clinical trial, use of 25mg/kg/day of DCA in MELAS patients resulted in peripheral nerve toxicity, which resulted in discontinuation and termination of study. Due to absence of any beneficial effects and potential role in nerve toxicity, DCA is not recommended to patients with MELAS and should be avoided in cases prone to development of peripheral neuropathy. (45)

Idebenone is an analogue of coenzyme Q that facilitates electron transfer.

Idebenone has been favourably used in LHON patients. A study on the effects of idebenone on fibroblasts of LHON patients showed marked improvement in the activity of complex I but showed variable effects on cell respiration suggesting that patients might not respond uniformly to this treatment (46)

## CONCLUSION:

Significant progress has been made in the understanding of beta cell function.

In general the broad details of insulin biosynthesis, secretion and glucose sensing system are well established. However large lacunae in our knowledge concerning the molecular details still remain. Complexities of cell specific and acute control of insulin gene expression are just beginning to unfold. The biochemical details targeting the insulin to the secretory granules still remain sketchy and our knowledge of secretory processes is still rudimentary.

During the last decade, the study of these monogenic syndromes has led to the identification of several genes that were not previously suspected to play a role in glucose metabolism. It is anticipated that more genes involved in insulin secretion or action will be identified by studying these forms of diabetes. Mitochondria, the centre of energy production and its metabolism represent itself as the central crossroad of various metabolic pathways.

One of the discussed metabolic pathways is insulin exocytosis and its secretory regulation where mitochondria generate the numerous signals that regulate the mediators of cellular excitability and insulin exocytosis from beta cell. Glucose stimulated insulin release from beta cell's mitochondria solely depends on ATP/ADP ratio and ROS production levels.

Increased ATP production and diminished ROS levels stimulates the insulin exocytosis from beta cells. But the disturbance in this ratio of ATP production to ROS levels along with defected mitochondrial morphology and biogenesis contributes to increased oxidative load to mitochondria or mitochondrial dysfunctioning which not only interferes with insulin secretion but also results in development of metabolic disorder like diabetes.

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